Journal of Pharmaceutical and Biomedical Analysis 134 (2017) 282–286

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

“Evaluation of ion mobility spectrometry for the detection of mitragynine in kratom products”

Nathan Fuenffinger, Melissa Ritchie, Ashley Ruth, Connie Gryniewicz-Ruzicka*

FDA, Division of Pharmaceutical Analysis, 645 S. Newstead, St. Louis, MO 63110, United States

ARTICLE INFO

Article history:
Received 7 June 2016
Received in revised form
28 November 2016
Accepted 30 November 2016
Available online 2 December 2016

Keywords:
Ion mobility spectrometry
Kratom
Mitragynine
Herbal supplements
Rapid screening

ABSTRACT

An ion mobility spectrometry (IMS) method was developed for the rapid detection of mitragynine, the most abundant alkaloid in *Mitragyna speciosa* also known as kratom. The peak corresponding to the mitragynine protonated ion exhibited a reduced ion mobility of $0.95 \pm 0.00014\,\text{cm}^2/(\text{V s})$, and the mitragynine limit of detection using IMS was 0.5 ng. The IMS method was applied to the analysis of 15 commercial samples suspected of containing kratom. IMS results were compared to those obtained from liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis of the same samples. Mitragynine was conclusively detected in 14 of 15 samples using LC–MS/MS and 13 of 15 samples using IMS. The discrepancy between methods reflected the fact that one sample contained mitragynine at a concentration below the IMS detection limit. This study demonstrates the utility of IMS for the rapid screening of products containing kratom as well as the scientific reliability of the IMS screening method, which was demonstrated by comparing the IMS results to the confirmatory results obtained using LC–MS/MS.

Published by Elsevier B.V.

1. Introduction

Mitragyna speciosa, a member of the Rubiaceae family, is a deciduous and evergreen tree indigenous to Southeast Asia. Commonly referred to as kratom, the plant has traditionally been used by natives for mainly recreational purposes [1]. A 2012 study carried out in Malaysia concluded that the majority of kratom users consume the drug in a moderate way, often as part of a social activity, for its stimulating effects [2]. Kratom use has not only been recreational, however, as the leaves have been used for many years to wean addicts off analgesic drugs such as morphine and heroin [3,4] and as a folk remedy for symptoms such as coughing, diarrhea, and muscle aches [5]. Nevertheless, the possession or selling of kratom leaves has been banned in countries such as Malaysia, Thailand, Myanmar, and Australia due to its narcotic effects [6]. In the U.S., kratom remains uncontrolled in most states and continues to be one of the legal drugs of choice for individuals seeking an alternative to opioids. The substance can be purchased over the internet as herbal products in the forms of leaves, powders, encapsulated powders, and extracts.

There is no established medical use for kratom in the U.S. Importation of kratom products has been noted by several U.S. government agencies. The U.S. Drug Enforcement Administration (DEA) currently lists kratom as a “Drug of Concern” [7]. DEA contends high doses of the substance can produce opiate effects and lead to addiction. The U.S. Food and Drug Administration (FDA) issued an import alert on kratom in February 2014. According to the FDA, kratom is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that it does not present a significant or unreasonable risk of illness or injury; therefore, dietary supplements containing kratom are classified as adulterated under the Federal Food, Drug and Cosmetic Act [8].

The *Mitragyna speciosa* plant may contain more than 25 alkaloids depending on the plants geographical location and season. Mitragynine is the most abundant of these alkaloids and its content can vary, ranging from 12% of the total alkaloid content in species originating in Malaysia to 66% for species grown in Thailand [9]. Kratom products can be identified using a variety of liquid chromatography (LC) and mass spectrometry (MS) methods. For example, LC electrospray ionization (ESI) MS [10] and direct analysis in real-time (DART) MS [11] methods have been developed for forensic screening of kratom in dried leaf, powder, and resin forms. To determine possible exposure to kratom, LC–MS^n methods have also been established for the identification of kratom metabolites in human and rat urine [12–18], as well as rat plasma [19]. The previously mentioned methods of analyses must be conducted in a laboratory and are often time consuming due to increased sample preparation and sample analysis times.

---

* Corresponding author.
E-mail address: connie.ruzicka@fda.hhs.gov (C. Gryniewicz-Ruzicka).

http://dx.doi.org/10.1016/j.jpba.2016.11.055
0731-7085/Published by Elsevier B.V.

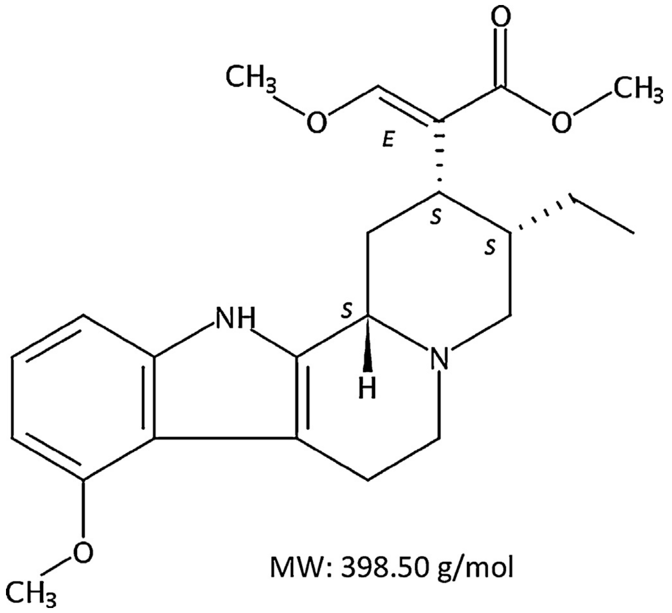

Fig. 1. Chemical structure of mitragynine.

To combat the presence of adulterated drug products in the marketplace, the FDA has started an initiative to develop rapid and reliable screening methods to assess the quality of food and drug products. One of the techniques used in the rapid screening program is ion mobility spectrometry (IMS). IMS can be used to provide rapid analyses of pharmaceuticals [20–31]. With the high sensitivity of IMS (detection at the ng level) and the availability of portable and compact instruments, samples can be analyzed on-site with sample analysis times (preparation time included) on the order of minutes making it a suitable technique for rapid drug screening.

The objective of this work is to demonstrate the feasibility of IMS as a rapid screening method for the detection of mitragynine (structure and molecular weight shown in Fig. 1), the main alkaloid present in kratom products. In this study, 15 commercial products suspected of containing mitragynine were collected and evaluated. The products were analyzed using the IMS screening method developed for the detection of mitragynine. The IMS results were compared against the LC–MS/MS analysis results for the same sample set in order to evaluate the performance of the IMS screening method against the confirmatory method.

2. Experimental

2.1. Materials

A 100 μg/mL mitragynine in methanol certified reference standard was purchased from Cerilliant (Round Rock, TX, USA). Fifteen samples labeled as kratom and suspected of containing mitragynine were obtained from the FDA/Office of Regulatory Affairs Forensic Chemistry Center. Optima LC–MS grade methanol, acetonitrile, water, and formic acid were purchased from Fisher Scientific (Fair Lawn, NJ, USA).

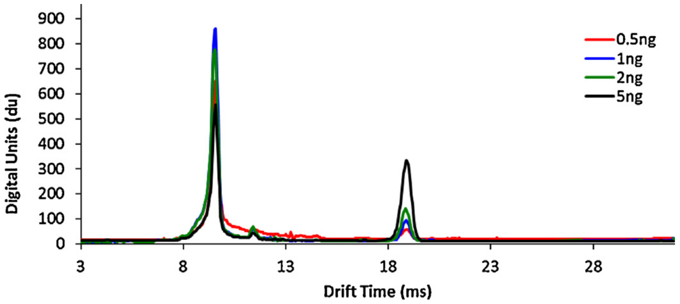

Fig. 2. Ion mobility spectra of mitragynine reference standards.

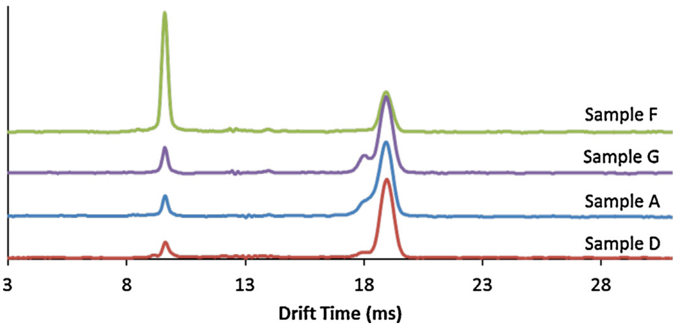

Fig. 3. Ion mobility spectra of representative kratom test samples.

2.2. Reference standards and sample preparation for IMS analysis

Mitragynine reference standard solutions were prepared for IMS analysis by diluting the 100 μg/mL certified reference standard with methanol to prepare a series of standards with concentrations over the range from 0.5–100 ng/μL.

The kratom samples were prepared for IMS analysis using one of four methods which differed slightly based on the form of the product (powder, liquid, capsule, or ground leaves). Solid and liquid samples were transferred to polypropylene centrifuge tubes and diluted with 15 mL of methanol. Initial sample amounts include one capsule for finished dosage forms, 250 μL for liquids, and ¼ teaspoon for powdered samples and leaf material. The samples were mixed by inversion for approximately one minute, and the solid particulates were allowed to settle for ~30 s. The supernatant liquid was filtered into a second centrifuge tube using a 0.45 μm PTFE filter and additional dilutions of 1:200 and 1:20 were prepared for bulk powder and finished dosage forms, respectively.

2.3. Reference standards and sample preparation for LC–MS/MS analysis

The LC–MS/MS procedure was adapted from a previously reported method from Casey et al. [32]. Briefly, a series of mitragynine reference standard solutions covering a range of concentrations from 10 to 100 ng/mL were prepared by diluting the 100 μg/mL certified reference standard with methanol. The limit of detection and the limit of quantitation of mitragynine using the LC–MS/MS method were determined based on ICH method validation guidelines and are 2 ng/mL and 6 ng/mL, respectively. Solid samples were prepared for LC–MS/MS analysis by transferring 100 ± 10 mg of sample into a 50 mL centrifuge tube. Samples were extracted with 10 mL of methanol, vortexed briefly and placed in an ultrasonic bath for 20 min. After sonication, samples were centrifuged at 3000 rpm for 10 min at 4 °C. The supernatant was decanted into a 10 mL volumetric flask and diluted to volume with methanol. The diluted samples were filtered using a 0.2 μm PTFE filter and the initial extracts were analyzed using LC–MS/MS. For samples containing concentrations of mitragynine above the upper limit of the calibration curve, further dilutions were prepared with dilution factors ranging from 1:100 to 1:20,000.

Table 1
Instrument parameters for ion mobility spectrometry.

Parameter	Value
Drift tube temperature	249 °C
Inlet temperature	291 °C
Desorber temperature	291 °C
Calibrant block temperature	74 °C
Drift flow	300 cc/min
Analysis time	14 s
Pulse width	0.2 ms
Scan period	32 ms
Sampling period	25 µs
Number of co-added scans per segment	10

Table 2
Mitragynine alarm parameters on the IONSCAN 500DT.

Parameter	Mitragynine
Reduced mobility (K_o)	0.9473 cm^2/(V s)
Positive and negative variability	100 µs
Amplitude threshold	30 digital units
Full width half maximum	480 µs
Number of sequential hits	2

2.4. Ion mobility spectrometry

Ion mobility data were acquired using an IONSCAN 500DT ion mobility spectrometer (Smiths Detection, Danbury, CT, USA) equipped with an internal nicotinamide calibrant that was continuously circulated through the system. Mitragynine was detected in positive ion mode using the parameters listed in Table 1. The analysis time of 14 s and the inlet and desorber temperatures of 291 °C are the optimized default values for a general drug screening method developed in-house. For IMS analysis, one µL of sample was deposited onto a Smiths 500DT Nomex dual mode (explosive and narcotic) swab, and the solvent was allowed to evaporate. The swab containing the sample was introduced into the system and placed on the desorber heater. Analyte molecules were vaporized and carried from the heated inlet to the ionization chamber in a flow of dry air carrier gas. The volatilized analyte molecules were ionized by a ^{63}Ni β source in a controlled chemical ionization environment to produce product ions. Analyte ion drift times were measured relative to the drift time of the internal nicotinamide calibrant. Analyte bands were identified visually and user selected for analysis by the 500DT Viewer Software version 2.06.008. The software fit the selected bands to a Gaussian shape, and reported the peak drift time (t_d), peak amplitude, peak area, and peak full width at half maximum (FWHM). Gained from these observations is a qualitative measure of the ions referred to as the ion mobility constant (K). Commonly, K is corrected to standard temperature and pressure to produce a reduced ion mobility constant (K_0) which relates the length (L) of the drift tube, the voltage across the drift region (V), and t_d:

$$K_0 = \frac{L}{Vt_d} \times \frac{P}{760} \times \frac{273}{T} \tag{1}$$

where P is the pressure in Torr, and T is the temperature in Kelvin [33]. When P=760 Torr and T=273.2 K, K_0=L/Vt_d. From Eq. (1), it is apparent that the $K_0 \cdot t_d$ is constant during the measurement of an ion mobility spectrum in a well-controlled environment. Therefore an internal calibrant with known ion mobility, $K_{0,C}$, can be used to provide accurate measurement of an analyte's ion mobility, $K_{0,A}$, from its drift time, $t_{d,A,}$ and the drift time of the internal calibrant, $t_{d,C,}$ using the following equation:

$$K_{0,A} = K_{0,C} \times \frac{t_{d,C}}{t_{d,A}} \tag{2}$$

The use of the internal calibrant obviates the influence of small variations in P, T and V that occur between measurements made on different days, and allows reduced ion mobilities to be used for qualitative analysis of analytes when analyte reference standard materials are available.

Ion mobility data acquired on the IMS instrument cannot be exported in a tabular format due to the design of the instrument by the manufacturer. For this reason, the ion mobility spectra were digitized using the UN-SCAN-IT software version 7.0 (Silk Scientific Corporation, Orem, UT, USA) for plotting and subsequent analysis.

2.5. Liquid chromatography–mass spectrometry

Samples were analyzed using an Agilent 1200 HPLC (Agilent Technologies, Inc., Wilmington, DE, USA) coupled to a Thermo VelosPro ion trap mass spectrometer (Thermo Scientific, Waltham, MA, USA). Samples were analyzed in positive ion mode. The ESI source conditions were as follows: spray voltage, 3.5 kV; sheath gas, 25 arbitrary units (AU); auxiliary gas, five AU. An MS/MS

Table 3
Comparison of the results for kratom products analyzed by IMS screening and LC–MS/MS analysis.

Sample	Type	IMS Screening Results						LC–MS/MS Results
		Pass/Fail	K_0 (cm^2/(V s))	FWHM (ms)	D_{time} (ms)	Area (du ms)	Amp (du)	Mitragynine Conc. (µg/mL)
A	Leaf	Fail	0.94 ± 0.0014	580 ± 98	18.896 ± 0.027	324.1 ± 143.4	209.5 ± 124.2	43.1 ± 1.8
B	Leaf	Fail	0.94 ± 0.00049	550 ± 23	18.916 ± 0.011	293.1 ± 14.3	171.6 ± 14.0	12.5 ± 0.4
C	Liquid	Fail	0.95 ± 0.00010	518 ± 21	19.017 ± 0.004	174.1 ± 36.6	96.5 ± 24.4	42.2 ± 1.4
D	Liquid	Fail	0.94 ± 0.000058	661 ± 11	19.038 ± 0.000	563.8 ± 25.9	399.9 ± 29.1	862 ± 2.4
E	Capsule	Fail	0.95 ± 0.00076	530 ± 14	18.994 ± 0.015	117.2 ± 3.3	66.1 ± 0.3	91.6 ± 1.4
F	Capsule	Fail	0.94 ± 0.00020	581 ± 9	18.994 ± 0.003	221.5 ± 66.6	137.5 ± 43.1	65.4 ± 1.4
G	Powder	Fail	0.94 ± 0.00027	637 ± 7	19.107 ± 0.005	504.6 ± 21.0	309.2 ± 48.3	694 ± 8.6
H1	Capsule	Fail	0.94 ± 0.00036	610 ± 26	19.007 ± 0.006	278.2 ± 52.9	181.6 ± 41.9	68.9 ± 2.2
H2	Powder	Fail	0.95 ± 0.00017	635 ± 7	19.079 ± 0.005	435.6 ± 28.5	294.4 ± 22.3	271 ± 0.2
I	Powder	Fail	0.95 ± 0.00027	600 ± 13	18.986 ± 0.006	354.4 ± 44.8	226.9 ± 44.8	115 ± 4.6
J	Capsule	Fail	0.94 ± 0.00099	580 ± 31	19.014 ± 0.019	318.8 ± 85.0	198.8 ± 85.0	85.1 ± 2.8
K	Capsule	Fail	0.95 ± 0.00046	566 ± 59	18.976 ± 0.009	247.5 ± 174.9	156.4 ± 127.0	72.5 ± 0.2
L	Capsule	Pass	*NA*	*NA*	*NA*	*NA*	*NA*	Not detected
M	Powder	Fail	0.95 ± 0.00052	580 ± 98	19.082 ± 0.007	666.2 ± 5.3	478.5 ± 2.4	505 ± 0.04
N	Capsule	Pass[a]	*NA*	*NA*	*NA*	*NA*	*NA*	0.03 ± 0.001

NA—Not Applicable (No mitragynine peak detected).

[a] Mitragynine concentration in sample below the LOD of the IMS method.

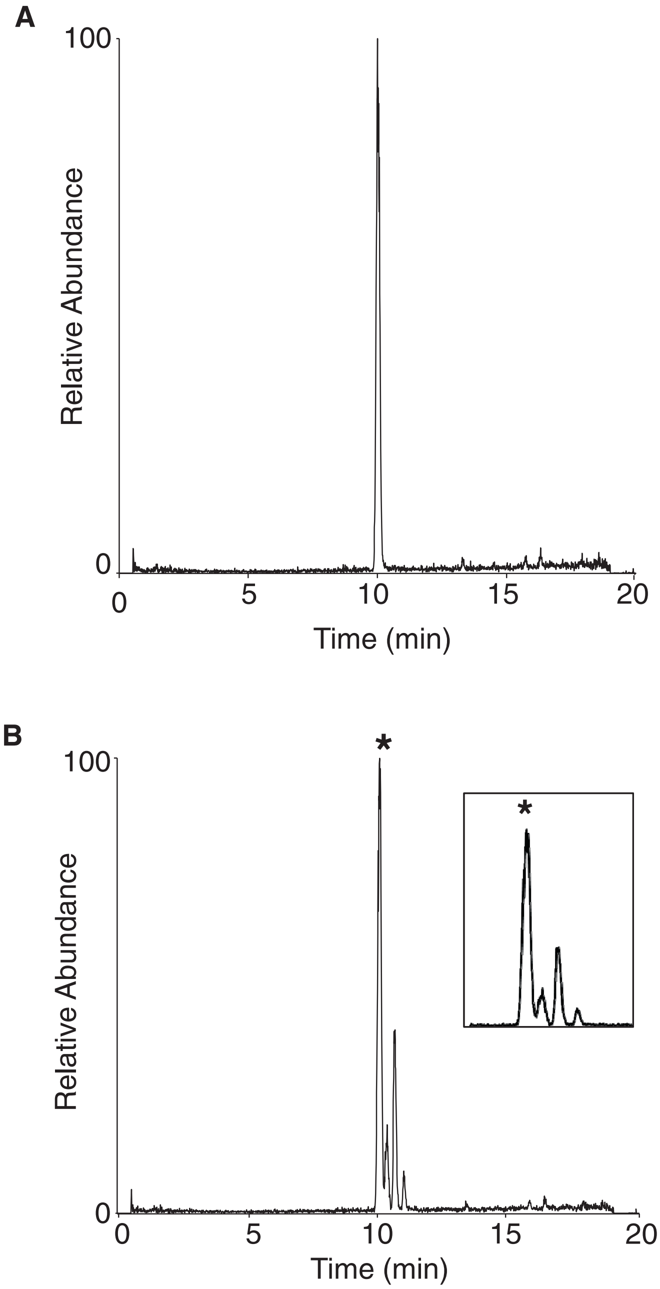

Fig. 4. Extracted ion chromatograms (399.2 m/z) of (A) 50 ng/μL mitragynine reference standard and (B) kratom sample in the form of ground leaves. Inset highlights the time range from 9 to 12 min. The (*) symbol identifies the peak corresponding to mitragynine in the sample.

step was included to confirm mitragynine identity: precursor ion, 399.2 m/z; isolation width, ± 3.0; collision energy, 35%; mass range, 105–500 m/z. A Waters XBridge C18 column (2.1 × 150 mm, 5 μm) was used with 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) as mobile phases and maintained at 35 °C. Injection volume for both standards and samples was 5 μL. The initial gradient composition was 90% A and 10% B, linearly increasing to 95% B over 15 min. Isocratic flow continued for two minutes at 95% B before returning to 90% A over 0.1 min for a 2.9 min re-equilibration period. Sample mitragynine concentrations were determined by LC–MS using the extracted ion chromatograms (EICs) of the mitragynine MH+ peak (m/z 399.2) with a ±0.5 m/z window. Data were analyzed using XCalibur QualBrowser software (Thermo, version 2.2) using the ICIS peak detection algorithm.

3. Results and discussion

The mitragynine reference standard was analyzed across a series of concentrations (0.1–5 ng/μL) with five replicates at each concentration in order to determine the reduced ion mobility and the peak parameters for the mitragynine alarm. Table 2 lists the alarm parameters set on the IMS instrument for the detection of mitragynine. Several criteria must be met for the mitragynine alarm to trigger on the IMS instrument. First, the variability sets a window in which a peak must occur to trigger an alarm on the instrument for amplitudes above the amplitude threshold and the detected peak must also be above the set amplitude threshold in at least two sequential segments. Additionally, the full width half max (FWHM) value was set to ensure that an alarm was obtained for mitragynine concentrations between a range of 0.5 ng to 100 ng. The ion mobility spectra for the mitragynine reference standards are shown in Fig. 2. The sharp peak observed at approximately 9.5 ms in all ion mobility spectra is attributed to the instrument's nicotinamide internal calibrant. The protonated ion peak for the mitragynine reference standard is observed at a drift time of 18.8 ± 0.006 ms, corresponding to a reduced ion mobility of 0.95 ± 0.00014 $\text{cm}^2/(\text{V}\bullet\text{s})$. The LOD for the mitragynine reference standard is 0.5 ng and was determined experimentally as the concentration of the reference standard solution that resulted in a peak with maximum amplitude of approximately 30 digital units (du) above the noise level which was determined as 10 du. No peaks were observed during the IMS analysis of reference standards with concentrations below 0.5 ng/μL.

Using the reduced ion mobility and the peak FWHM value (480 μs) obtained in the analysis of the reference standard, an alarm was programmed on the IMS instrument for the detection of mitragynine. The mitragynine alarm will only activate during the analysis of a test sample if a peak with a similar reduced ion mobility as the mitragynine reference standard is detected that also meet the alarm criteria outlined in the experimental section.

Kratom products are sold in a wide variety of forms including powdered leaves, processed leaves, leaf extracts, liquids made of leaf extracts and capsules. As a result of these different forms, kratom products can vary in their mitragynine concentration. To ensure that mitragynine is detected in all types of kratom products and to prevent the saturation of the drift tube resulting in contamination of the instrument, four separate sample preparation procedures were developed and are detailed in the experimental section. Each of the preparation procedures began with a simple methanol extraction process. The extraction procedure reduced the contribution of interferents associated with the different sample matrices. After filtration, the methanol extraction for both liquid and leafy materials was analyzed "as is". Additional dilutions of the filtered methanol extracts were required for both bulk powder and capsule products since these forms have been shown to have a higher mitragynine concentration. In each of the established sample preparation methods, a constant volume of one μL of either the filtered extract or dilution solution is spotted on a swab and introduced into the IMS for analysis.

Fifteen test samples suspected of containing kratom were obtained and analyzed using the IMS screening method developed for the detection of mitragynine. Each sample is designated with a letter A-N. Samples labeled H1 and H2 indicate two products with the same name in capsule and powdered forms, respectively. The samples were also analyzed using LC–MS/MS for confirmation of the presence of mitragynine as well as quantitation. The IMS and LC–MS/MS results for the 15 samples are listed in Table 3. Samples "failed" IMS screening and were classified as positive for the presence of mitragynine when the mitragynine alarm triggered. The average ion mobility spectra for four suspect kratom samples of different forms are offset and shown in Fig. 3. Sample A is a ground leaf material, sample D is a liquid extract, sample F is a finished product distributed in a capsule form, and sample G is a bulk powder. The mitragynine alarm triggered during the IMS analysis of 13 of the 15 suspect kratom products, and two samples passed IMS analysis. No mitragynine was detected in sample L by IMS or LC–MS/MS analysis. Sample N was shown by LC–MS/MS to contain mitragynine at a concentration level below the LOD of the IMS screening method. Unresolved peaks at 18.2 ± 0.1 ms with an approximate reduced ion mobility of $0.99 \pm 0.0054\ \text{cm}^2/(\text{V}\bullet\text{s})$ were observed in the mobility spectra for kratom samples in all dosage forms analyzed by IMS that tested positive for the presence of mitragynine. These peaks can be attributed to additional alkaloids present in the *Mitragyna speciosa* plant. In addition to mitragynine, three additional indole alkaloid components are also commonly detected in kratom products. These species include speciogynine and speciociliantine, both of which are isomeric to mitragynine, as well as paynantheine, which are present in approximate proportions of 6.6, 0.8 and 8.6%, respectively. Fig. 4 shows an extracted ion chromatogram for the mitragynine reference standard and a kratom sample in the form of ground leaves. The isomeric forms of mitragynine were detected and resolved from one another in the LC–MS/MS analysis of the kratom samples.

4. Conclusion

An IMS method has been developed and used to rapidly screen products suspected of containing kratom. An alarm for mitragynine was programmed onto a compact IMS instrument using several parameters determined based on the analysis of a certified reference standard. An optimized LC–MS/MS method was also developed that could both confirm the identity and quantitate the amount of mitragynine present. Thirteen of the 15 samples in the sample set contained mitragynine at levels above the IMS detection limit, corresponding to a 100% success rate for positive identification of mitragynine. No false positives were obtained based on the sample set analyzed in this study. One additional sample was found by LC–MS/MS analysis to contain mitragynine below the IMS detection limit. This work demonstrates the suitability of IMS to be used as a rapid screening technique for kratom products and/or products purported to contain mitragynine.

References

[1] K.B. Chan, C. Pakiam, R.A. Rahim, Psychoactive plant abuse: the identification of mitragynine in ketum and ketum preparations. In: Bulletin on Narcotics: Science in Drug Control: the Role of Laboratory and Scientific Expertise, S. Chawla, Ed., United Nations, New York, 2007, vol. LVII, p. 249.
[2] K. Ahmad, Z. Aziz, Mitragyna speciosa use in the northern states of Malaysia: a cross-sectional study, J. Ethnopharmacol. 141 (2012) 446–450.
[3] K.S. Grewal, The pharmacology of mitragynine, J. Pharmacol. 46 (1932) 251–271.
[4] B. Vicknasingam, S. Narayanan, G.T. Beng, S. Mansor, The informal use of ketum (Mitragyna speciosa) for opioid withdrawal in northern states of peninsular Malaysia and implications for drug substitution therapy, Int. J. Drug Policy 21 (2010) 283–288.
[5] C. Ulbricht, D. Costa, J. Dao, R. Isaac, Y.C. LeBlanc, J. Rhoades, R.C. Windsor, An evidence-based systematic review of kratom (Mitragyna speciosa) by the Natural Standard Research Collaboration, J. Diet. Suppl. 10 (2013) 152–170.
[6] J.E. Adkins, E.W. Boyer, C.R. McCurdy, Mitragyna speciosa, a psychoactive tree from southeast Asia with opioid activity, Curr. Top. Med. Chem 11 (2011) 1165–1175.
[7] U.S. Drug Enforcement Administration Drugs of Abuse, 2015, edition. http://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf, (Accessed Mar. 07, 2016).
[8] U.S. Food and Drug Administration Import Alert 54-15, http://www.accessdata.fda.gov/cms_ia/importalert_1137.html, (Accessed Apr. 01, 2016).
[9] S. Parthasarathy, S. Ramanathan, V. Murugaiyah, M.R. Hamdan, M.I.M. Said, C. Lai, S.M. Mansor, A simple HPLC-DAD method for the detection and quantification of psychotropic mitragynine in *Mitragyna speciosa* (ketum) and its products for the application in forensic investigation, For. Sci. Int. 226 (2013) 183–187.
[10] R. Kikura-Hanajir, M. Kawamura, T. Maruyama, M. Kitajima, H. Takayama, Y. Goda, Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant kratom (*Mitragyna speciosa*) by LC-ESI–MS, Forensic Toxicol. 27 (2009) 67–74.
[11] A.D. Lesiak, R.B. Cody, A.J. Dane, R.A. Musah, Rapid detection by direct analysis in real time-mass spectrometry (DART-MS) of psychoactive plant drugs of abuse: the case of Mitragyna speciosa aka Kratom, For. Sci. Int. 242 (2014) 210–218.
[12] T. Arndt, U. Claussen, B. Güssregen, S. Schröfel, B. Stürzer, A. Werle, G. Wolf, Kratom alkaloids and O-desmethyltramadol in urine of a Krypton herbal mixture consumer, For. Sci. Int. 208 (2011) 47–52.
[13] S. Lu, B.N. Tran, J.L. Nelsen, K.M. Aldous, Quantitative analysis of mitragynine in human urine by high performance liquid chromatography-tandem mass spectrometry, J. Chromatogr. B 877 (2009) 2499–2505.
[14] A.A. Philipp, D.K. Wissenbach, S.W. Zoerntlein, O.N. Klein, J. Kanogsunthornrat, H.H. Maurer, Studies on the metabolism of mitragynine, the main alkaloid of the herbal drug Kratom, in rat and human urine using liquid chromatography-linear ion trap mass spectrometry, J. Mass Spectrom. 44 (2009) 1249–1261.
[15] A.A. Philipp, D.K. Wissenbach, A.A. Weber, J. Zapp, S.W. Zoerntlein, J. Kanogsunthornrat, H.H. Maurer, Use of liquid chromatography coupled to low- and high-resolution linear ion trap mass spectrometry for studying the metabolism of paynantheine, an alkaloid of the herbal drug Kratom in rat and human urine, Anal. Bioanal. Chem. 396 (2010) 2379–2391.
[16] A.A. Philipp, D.K. Wissenbach, A.A. Weber, J. Zapp, H.H. Maurer, Metabolism studies of the Kratom alkaloids mitraciliatine and isopaynantheine, diastereomers of the main alkaloids mitragynine and paynantheine, in rat and human urine using liquid chromatography-linear ion trap-mass spectrometry, J. Chromatogr. B 879 (2011) 1049–1055.
[17] A.A. Philipp, D.K. Wissenbach, A.A. Weber, J. Zapp, H. Maurer, Phase I and II metabolites of speciogynine, a diastereomer of the main Kratom alkaloid mitragynine, identified in rat and human urine by liquid chromatography coupled to low-and high-resolution linear ion trap mass spectrometry, J. Mass Spectrom. 45 (2010) 1344–1357.
[18] A.A. Philipp, D.K. Wissenbach, A.A. Weber, J. Zapp, H.H. Maurer, Metabolism studies of the Kratom alkaloid speciociliatine, a diastereomer of the main alkaloid mitragynine, in rat and human urine using liquid chromatography-linear ion trap mass spectrometry, Anal. Bioanal. Chem. 399 (2011) 2747–2753.
[19] P.K. Vuppala, S.P. Boddu, E.B. Furr, C.R. McCurdy, B.A. Avery, Simple, sensitive, high-throughput method for the quantification of mitragynine in rat plasma using UPLC-MS and its application to an intravenous pharmacokinetic study, Chromatographia 74 (2011) 703–710.
[20] A.H. Lawrence, Ion mobility spectrometry mass-spectrometry of some prescription and illicit drugs, Anal. Chem. 58 (1986) 1269–1272.
[21] A.H. Lawrence, Characterization of benzodiazepine drugs by ion mobility spectrometry, Anal. Chem. (1989) 343–349.
[22] G.A. Eiceman, D.A. Blyth, D.B. Shoff, A.P. Snyder, Screening of solid commercial pharmaceuticals using ion mobility spectrometry, Anal. Chem. 62 (1990) 1374–1379.
[23] M.A. Strege, J. Kozerski, N. Juarbe, P. Mahoney, At-line quantitative ion mobility spectrometry for direct analysis of swabs for pharmaceutical manufacturing equipment cleaning verification, Anal. Chem. 80 (2008) 3040–3044.
[24] M. Strege, Total residue analysis of swabs by ion mobility spectrometry, Anal. Chem. (2009) 4576–4580.
[25] R.M. O'Donnell, X. Sun, P.B. Harrington, Pharmaceutical applications of ion mobility spectrometry, TrAC Trends Anal. Chem. 27 (2008) 44–53.
[26] R. Fernandez-Maestre, H.H. Hill, Ion mobility spectrometry for the rapid analysis of over-the-counter drugs and beverages, Int. J. Ion Mobility Spectrom. 12 (2009) 91–102.
[27] C.M. Gryniewicz, J.C. Reepmeyer, J.F. Kauffman, L.F. Buhse, Detection of undeclared erectile dysfunction drugs and analogues in dietary supplements by ion mobility spectrometry, J. Pharm. Biomed. Anal. 49 (2009) 601–606.
[28] C. Qin, A. Granger, V. Papov, J. McCaffrey, D.L. Norwood, Quantitative determination of residual active pharmaceutical ingredients and intermediates on equipment surfaces by ion mobility spectrometry, J. Pharm. Biomed. Anal. 51 (2010) 107–113.
[29] J.D. Dunn, C.M. Gryniewicz-Ruzicka, J.F. Kauffman, B.J. Westenberger, L.F. Buhse, Using a portable ion mobility spectrometer to screen dietary supplements for sibutramine, J. Pharm. Biomed. Anal. 54 (2011) 469–474.
[30] J.D. Dunn, C.M. Gryniewicz-Ruzicka, D.J. Mans, L.C. Mecker-Pogue, J.F. Kauffman, B.J. Westenberger, L.F. Buhse, Qualitative screening for adulterants in weight-loss supplements by ion mobility spectrometry, J. Pharm. Biomed. Anal. 71 (2012) 18–26.
[31] D.J. Mans, R.J. Callahan, J.D. Dunn, C.M. Gryniewicz-Ruzicka, Rapid-screening detection of acetildenafils, sildenafils, and avanafil by ion mobility spectrometry, J. Pharm. Biomed. Anal. 75 (2013) 153–157.
[32] C.R. Casey, T. Conley, A. Heise, T. Thomas, P.R. Ayres, Quantitative and qualitative analysis of mitragynine in Kratom (Mitragyna speciosa) by GC–MS, LC-MS/MS and UPLC-PDA, J. Regul. Sci. 2 (2015) 1–14.
[33] E.A. Mason, H.W. Schamp, Mobility of gaseous ions in weak electric fields, Ann. Phys. 4 (1958) 233–270.